Trends Towards the Industrialization of Quantitative Systems Pharmacology in Drug Research & Development

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Disclosures & Acknowledgements

- I am an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and shareholder of Merck & Co., Inc., Kenilworth, NJ, USA

- Ideas and concepts here from colleagues at the research laboratories of Merck & Co., Inc., Kenilworth, NJ, USA

- IQ QSP WG
- Brian Topp for his concepts around Virtual Patients and Tumor growth
- Vantage and Atomic Veggie for IO QSP and Visualization
- Examples: Published and accordingly attributed

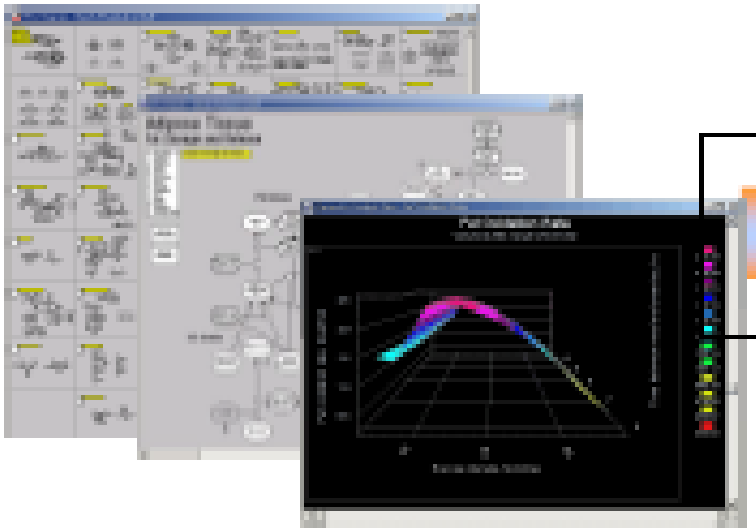
Outline

- General Trends with QSP in industry
- The Natpara® example – “Watershed” or a fond memory?
- Learnings with PBPK
- What does it take? – e.g. Immuno-Oncology
- Challenges

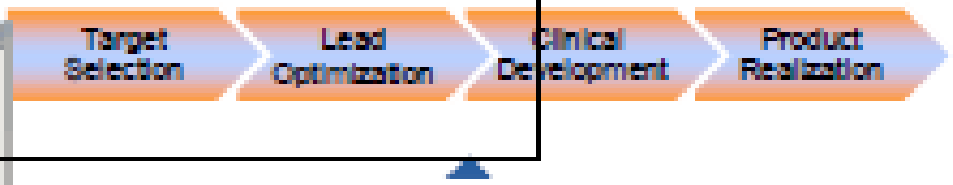
A Look Back…Pioneers at Entelos, Inc

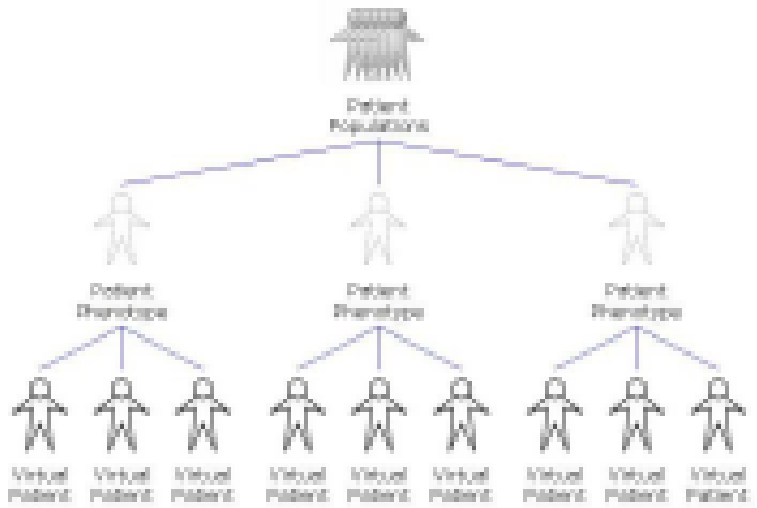
Mechanistic Description of Biological Systems

Large-scale models that detail physiology and explicitly/implicitly represent targets



…to predict human response and trigger experiments that test hypotheses





to simulate human physiology and create virtual patients….

Adapted: Entelos

Industrialization of QSP

1. Various consortiums, white papers, working groups, conferences or webinars focusing on quantitative and systems modeling (e.g. *QSP Workshops organized by NIH in 2008 and 2010; Rosa's Worldwide Webinar Series; QSP Webinar organized by IQ CPLG; International Society of Pharmacometrics (ISoP) QSP Special Interest Group; QSP sessions at American Conference on Pharmacometrics, Discovery on Target and QSP topics organized by American College of Clinical Pharmacology (ACCP), American Association of Pharmaceutical Scientists (AAPS) Quantitative Pharmacology Task Force, American Society for Clinical Pharmacology and Therapeutics (ASCPT)*

2. Systems and mathematical-based training programs

3. Industry examples of QSP based modeling (Dr. Magee's presentation)

4. "Acceptance" of quantitative systems pharmacology (QSP) models by regulators

General Trends[1]

Based on company size, mid-large Pharma were more likely to describe some of their modeling activities as QSP (~ 25% do not label with QSP)

No company solely uses platform models. *Combination of* fit-for-purpose and platform models.

Neuroscience, Oncology and Autoimmune disorders are the three TAs with the most investment. Neuroscience is expected to have the most growth in QSP followed by continued investments in Oncology and Autoimmune disorders. [Worth noting advancements in Diabetes/Cardiovascular Disease as motivating examples]

Need for technical training, as well as the need to develop soft skills (like communication, leadership and project management), terminology, best-practices.

[1]Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape. In Press.

VISION

Industrialization of QSP Modeling in R&D

Vision

- Make QSP modeling a standard part of portfolio prioritization and decisions
- *When opportunity presents use QSP for regulatory decision-making*

Approach

- Develop QSP models in core disease areas (each organization will have focus areas)
- Leverage QSP modeling to project the probability of technical success (pTS)

Requirements

- Standard, pre-competitive, models of pathophysiology – public, qualification?
- Standard operating procedures for QSP model development, and application
- Integration of QSP modelers into discovery/development teams
- Integration of QSP modeling into governance documents/meetings

Questions for Systems Pharmacology

- Can we construct models ("fit for purpose") to generate mechanistic *and* testable biological hypotheses on therapeutic and safety profiles ?

— *Merits of pursuing a pharmacological target*

— *Decisions around patient stratification to individualization*

— *Selection and choice of combination treatments*

- What types of nonclinical *and* clinical data, information, tools, are needed to build these models and how should "confidence" be developed amongst stakeholders?

The Natpara® Example

Metabolic and Endocrine Parathyroid Hormone (Ind. Hypoparathyroidism) – Sep, 2014

Review - A system pharmacology approach applied to recommend an alternate dosing regimen

"..described their votes as "on the fence", …general belief that the company conducted its pharmacokinetic/pharmacodynamic study too late in the game leading to less than adequate dosing being brought forward in Phase III and for approval" – Pink Sheet, September 16 2014

Use of a Systems Pharmacology Model Based Approach Toward Dose Optimization of Parathyroid Hormone Therapy in Hypoparathyroidism. Clin. Pharmacol. Ther., 105: 710-718. 2019

What Happened in this *Rare* Example?

A mechanistic approach was needed and <u>question was clear</u>

Regulatory Drivers (Spontaneous collaboration)

Available mathematical model[1] of the pertinent physiology – calcium homeostasis (had not experienced any regulatory visibility although likely used in variety of internal decision by drug researchers for other indications).

- ❑ Understanding of the system (quantitative)

  +

- ❑ Understanding of the drug (quantitative)

- ➢ Simulate what we expect to see with alternative regimens, patient populations and combination treatments

[1]Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.

Pragmatism with Regulatory Filings

- **Some trends towards modest use (IQ Survey) in regulatory filings**
  - **Patient segmentation**
  - **Extension to indications**

- **High value proposition in rare diseases where limits to subject availability (evidence of effectiveness based on MoA?)**

Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa Is an Innovative Tool for Linking Pathophysiology and Pharmacology
CPT Pharmacometrics Syst. Pharmacol. 2017

Significant strides with Physiologically based Pharmacokinetic Models – Learnings?

Complex, and systematic move towards establishing predictive confidence

- Drug Interactions[1]
- Pharmacokinetics in pediatrics[2] …….

Finite number of “platforms” which have seen systematic development and curation

Increase in worldwide regulatory acceptance, many with the results that obviate the need for clinical trials

“Easier” to think about drug concentrations versus. outcomes

Emerging natural extensions as target engagement at site of action

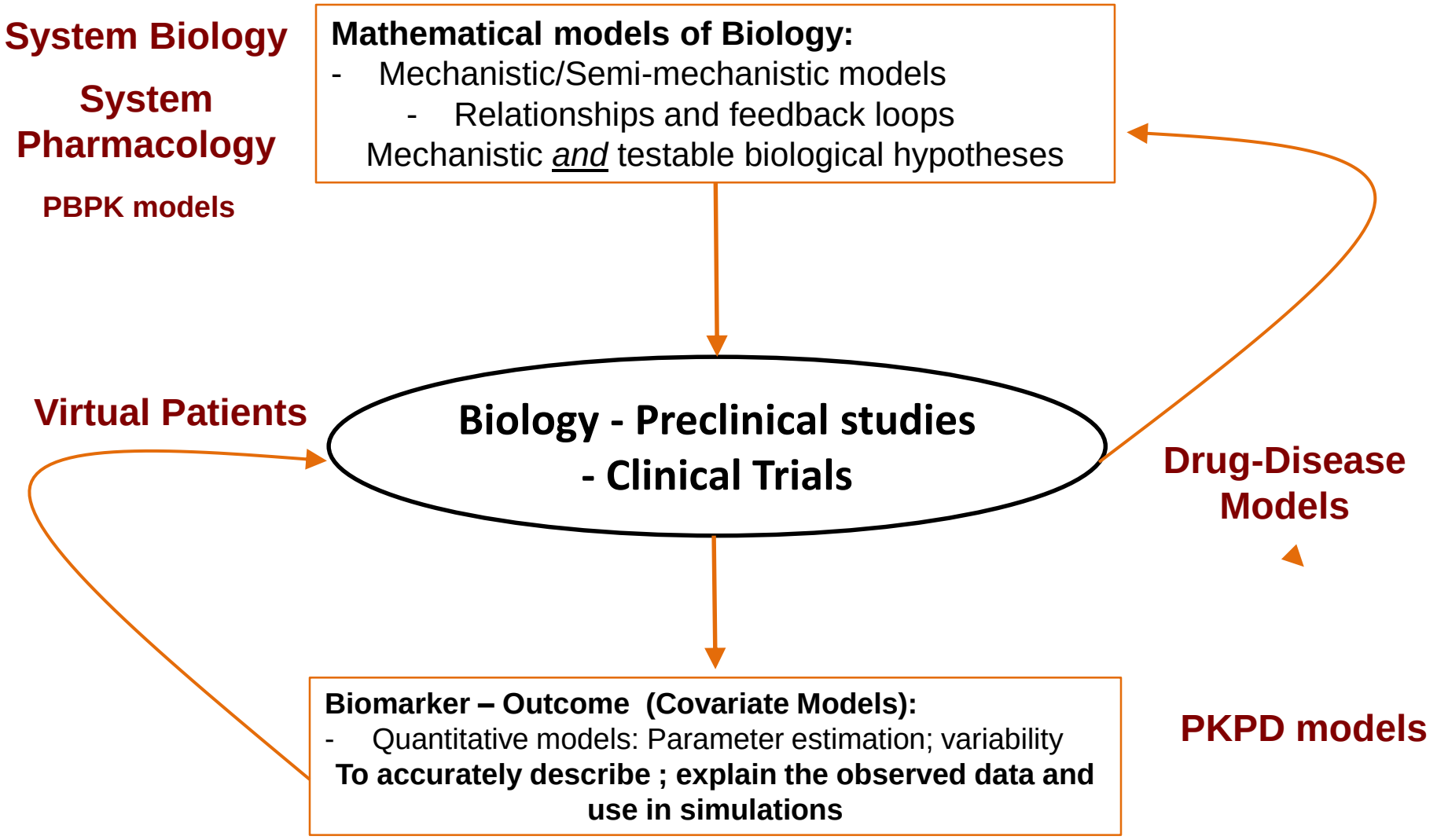
1CPT Pharmacometrics Syst Pharmacol. 2015 Apr; 4(4): 226–230.
[2] Clin. Pharmacol. Ther., 104: 188-200.2017

Progression of Models

(Particularly well exemplified with the treatment of Diabetes)

Model	Components	Model Evaluation
System Biology – Pathway models	Pathway Parameters; Simulation Models	Belief, biological plausibility, experimental data. Sensitivity Analysis
Systems Pharmacology	Pathway Parameters; Simulation Models (Few estimate)	Belief, biological plausibility, experimental data. Sensitivity Analysis/Alternate Hypothesis (Observed)
Covariate -PK-PD-Outcomes-Trial	**Structure, Parameters, Variability (Simulation and Estimation Models)**	**Belief, biological plausibility, experimental data, Pharmaco-statistical approaches**

Aim: Transform drug discovery and knowledge cycles



QSP Modeling

What are we Trying to Accomplish

Applications

Projecting the probability of technical success for novel Rx
Identifying responder populations
Dose justification

Methodology

Develop a mathematical model of a disease process (Virtual Patients)
Integrate a novel therapy into the model
Simulate a trial

Outcomes

1. Projected efficacy based on our present understanding of human pathophysiology
2. A transparent summary of data and assumptions used to generate the projection
3. A platform to test assumptions and alternative hypotheses

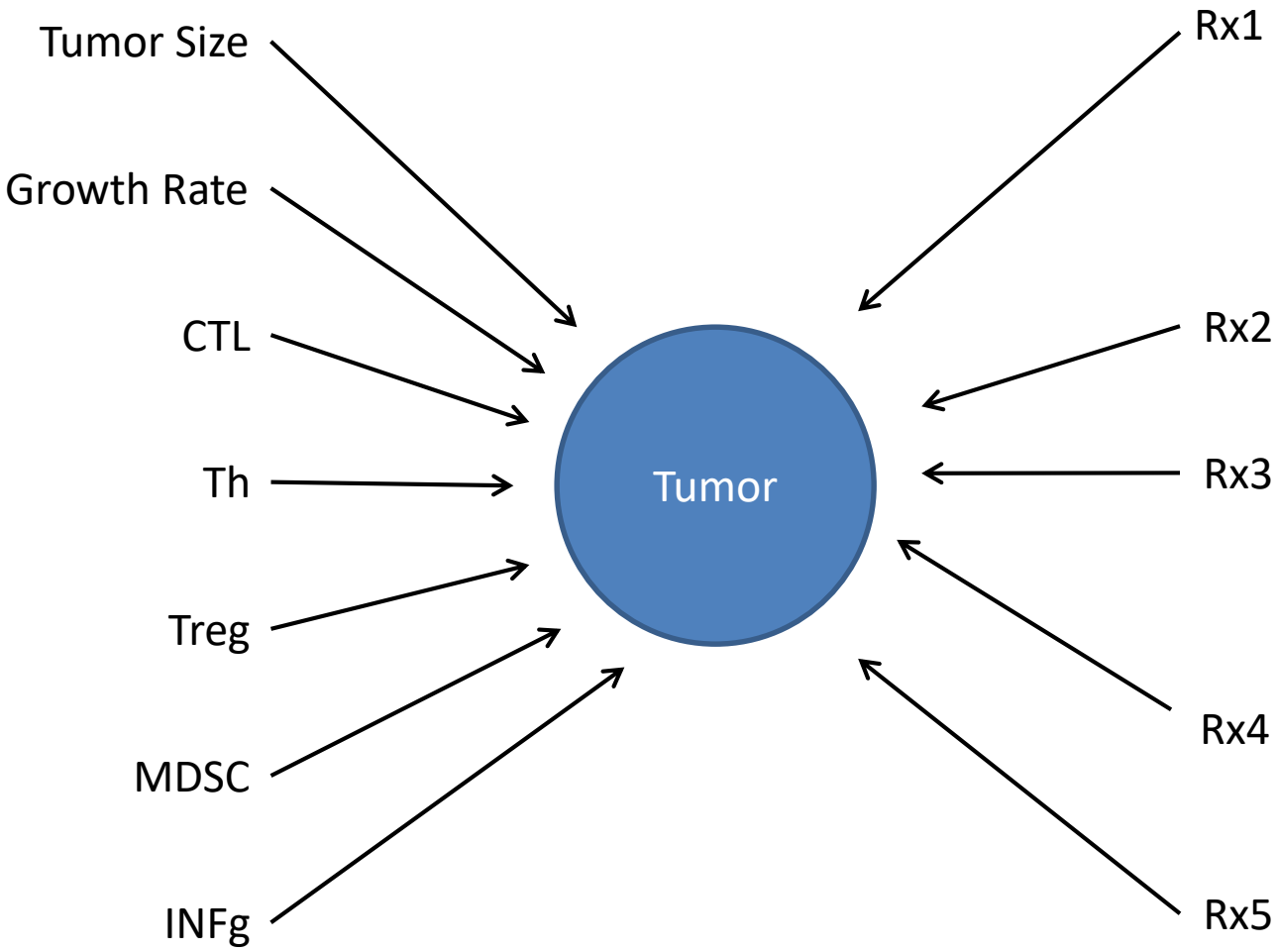
Predicting response and identifying responders to combination Cancer Immunotherapy in using Quantitative Systems Pharmacology (QSP) models – Melanoma as an Example

Contributors: Vantage Research
Presented at PAGE 2018

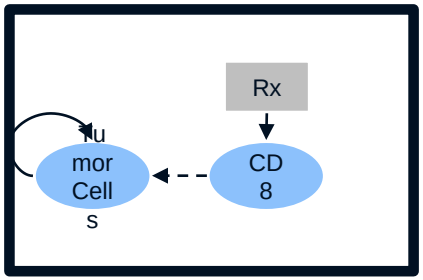
Merck Research Laboratories

Creating Virtual Tumors

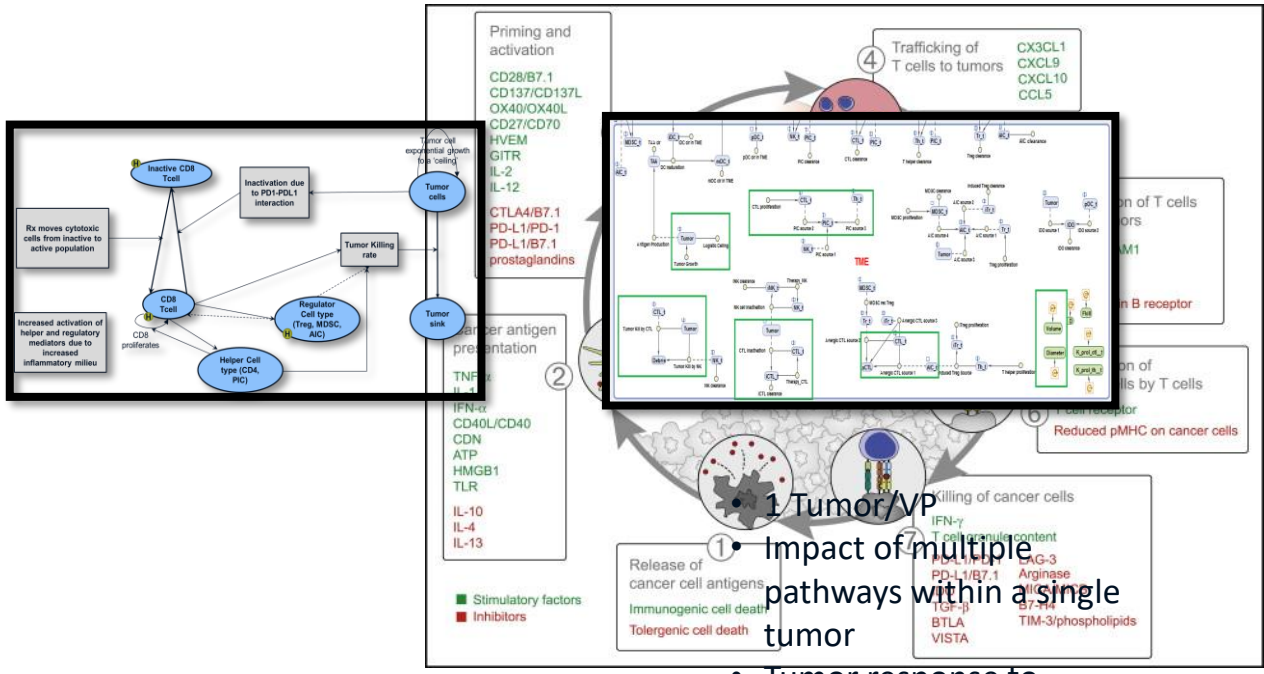
Complex pathophysiology and Multiple Rx Inputs



Approach to Model Design Varies With the Question



- 5 tumors/ VP
- Impact of within patient tumor heterogeneity, metastases
- Tumor 'waterfall' plots & RECIST scores
- **Ideal to simulate clinical trials**

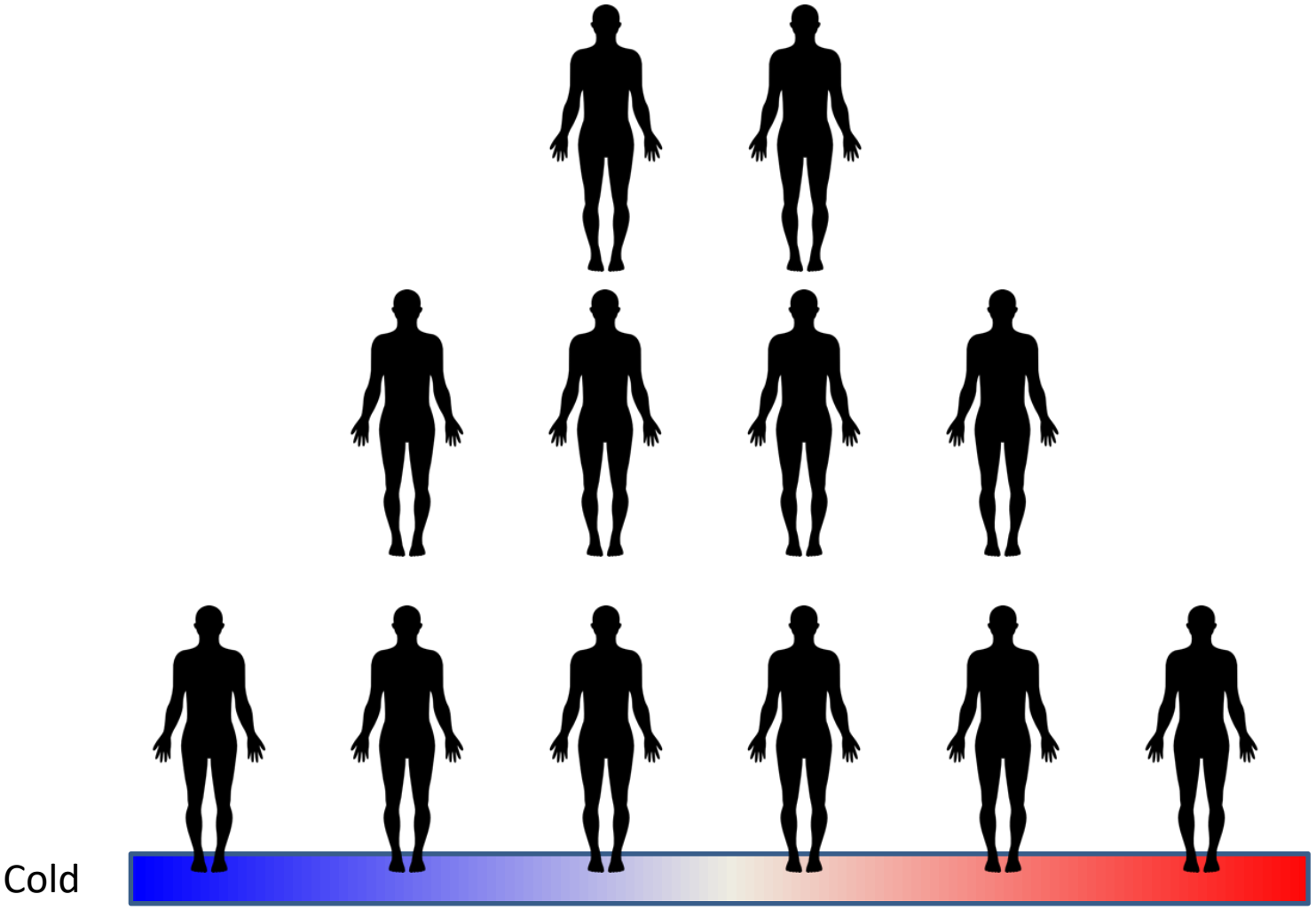


- 1 Tumor/VP
- Impact of multiple pathways within a single tumor
- Tumor response to treatment
- **Ideal to prioritize/ simulate targets in discovery**

Chen and Mellman, Immunity 2013

Creating Virtual Populations

e.g. Cancer Types, Stage of Disease, Biomarker Classes



Kumar et al, PAGE 2018

Model quantification and assimilation of the public literature

What are the kinds of data that are used to constrain the model ?

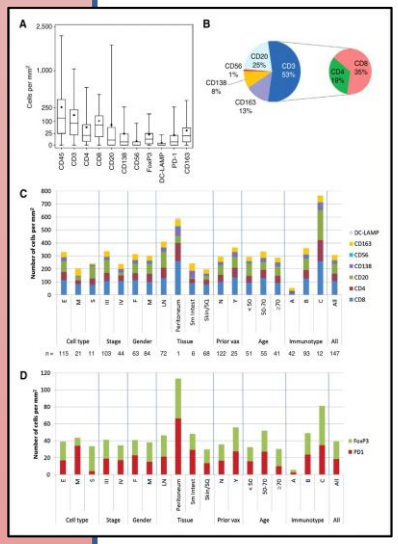
1. Overall tumor volume, estimated from cell densities and used to estimate cell numbers; directly from melanoma literature
2. Initial condition, clearance rates, proliferation rates for cell types from multiple papers
3. Best available information on interaction between these components that can usually only be obtained from experimental data[1]

- **1000s of Papers**
- **100s of papers documented,**
- **10s of papers used for direct parametrization**

➢ **Recorded for future evaluation as needed**

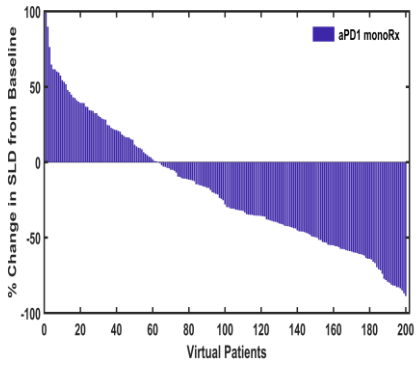
Relevant, Reliable
Used as-is

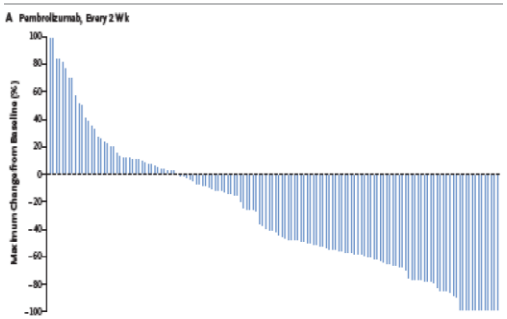
Used for initial parameterization
Adjusted to fit clinical time-course data



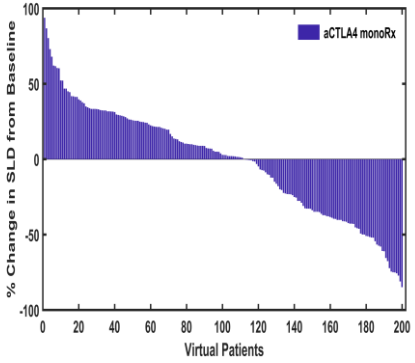
[1]Erdag et al 2012, data from > 100 HUMAN, MELANOMA BIOPSIES

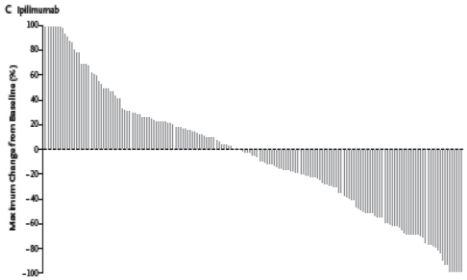
Virtual Population calibrated to match aPD1 and aCTLA4 clinical data





Robert et al., NEJM, 2015
Pembrolizumab

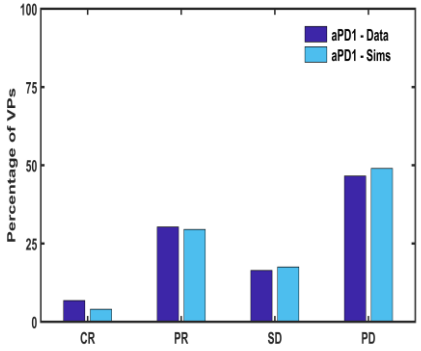




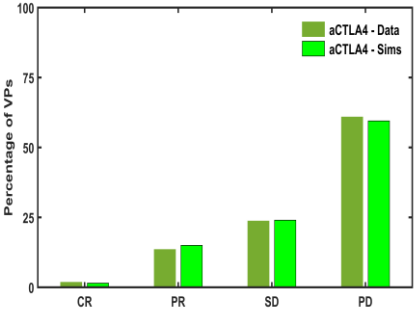
Robert et al., NEJM, 2015 Ipilimumab

SIMULATIONS

DATA



DATA vs. SIMULATIONS



Evolution of QSP Modeling

Models, Visualization

Large platform models

- Expensive, transparency (commercial), time consuming
- Attempt to explain everything lead to models with more assumptions than facts

Small, Modular, Plug-n-Play models

- As simple as possible … but no simpler
- Predictive capacity is limited by the boundary conditions
  - ex. a glucose only model does not predict drug effect on hepatic lipid accumulation

Intuitive, interactive, apps

- Allows for visualization of complex systems
- Allows non-math experts to use QSP models
- Allows for truly cross disciplinary research (everyone can use the model)

The Challenge

- **Varied use of quantitative systems pharmacology in drug research and development – clearly being used in decision making at various stages of R&D**
- **Computational capability is high - universality of platforms and common vocabulary is lacking**
- **With regulatory filings, small "n" however, this cannot be a reason not to appropriately use a systems approach**
- **Value proposition is constantly debated**
- **Drawing parallels to similar predictive approaches (PKPD, PBPK), a systematic approach towards industrialization is needed**

Who needs to be convinced? and how?

Discovery Sciences, Clinicians (and decision makers)

Largely artificial divide between "systems" approaches and "PK/PD" scientists – when the question is relevant – one is a logical extension

Can only be tackled at therapeutic/indication level by integration of data and assessing predictive performance

Summary

- As noted in the survey, wide use of QSP in the industry
  - clearly being used in decision making
  - In new drug submissions, predictive power of system pharmacology models must be properly assessed
- Establishment of Good Practices
- Qualification (i.e., EMA) is one possible route
- Learnings from Industrialization and Adoption of Population Approaches, PBPK